NEONATAL PAIN

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The traditional view has been that human neonate and fetus is not capable of perceiving pain and thus they were being subjected to invasive procedures and surgery without analgesia/anesthesia(1). Some of the reasons given in support of this pervasive view were: (*a*) Complete myelination of pain fibres is necessary for transmission of pain impulses. As the neonatal nerves are non-myelinated, the sensation of pain cannot be perceived(2); (*b*) Neonates do not have memories of painful experience thus they are not capable of responding to pain(3); (*c*) Newborn is unable to report pain and does not exhibit appropriate responses to painful stimuli(4); and (*d*) Neonatal responses to pain are decorticate in nature and perception or localization of pain is not present(5).

Current Thinking

With the growing body of research and evidence gathered, the above assumptions seem to be no more tenable and the ability of newborn to experience pain is gaining recognition. It is important to realize that newborns not only experience pain and stress but their pain responses may even influence their subsequent social and behavioral development.

We now know that spinal nerve tracts carrying pain impulses get myelinated *in utero*(6,7). Moreover, pain impulses are mainly carried by unmyelinated (C-polymodal) and thinly myelinated (A-δ) fibres. This indicates that complete myelination is not a necessary pre-requisite for transmission of pain impulses as thought earlier.

It is well established now that fetus can learn and respond as per prior exposure to various stimuli, and this encompasses the development and organization of various sensory systems including pain. Further, newborns who undergo painful procedures seem to develop a higher threshold for subsequent nociceptive activity as compared to their counterparts who have not experienced pain in the fetal/neonatal period. Also, newborns have a well developed and functioning limbic system and diencephalon; needed not only for a long term memory but instrumental in providing effective dimension to the sensory discriminative component of pain. Early painful experiences are stored though they may not be accessible to conscious recall(8-11).

Poorly developed verbal skills for reporting pain in neonates has created a false impression that neonates do not respond to pain. Recently, pain experience in neonates is receiving systematic studies. Cardiopulmonary changes, acoustic analysis of cry and studies of facial expressions form the

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basis of non-verbal distress during pain in neonates(9,12,13).

At the same time, human newborn has an anatomically and functionally developed sensory cortex as evidenced by description to follow and it may not be necessary to just postulate a subcortical mechanism for pain appreciation. Moreover, presence of various cognitive, coordinative and associative capabilities in both term and preterm babies leave no doubt about the involvement of cortical functioning.

Maturation of Fetal Pain Pathways

(*a*) *Anatomical Development*

The pain impulses travel from the peripheral skin receptors to the different levels of neuraxis including cortical regions of the brain. Neonatal skin shares the similar density of cutaneous nerve endings as in adults. These nerve endings first appear in the peri-oral region by 7th week of gestation. By 11th week rest of the face, palm and soles are also innervated. Trunk, proximal arms and legs get their receptors by the end of 15th week. By 20th week of intrauterine life, synapses form between sensory fibres and dorsal horn of spinal cord alongwith completion of innervation process. Various cells of dorsal horn form and arrange themselves in adult fashion by 30th week of gestation. Development of fetal neocortex and thalamocortical pathways, crucial for cortical pain perception, takes place before the completion of second trimester of pregnancy(1,14,15).

(*b*) *Functional Development*

Myelination: Pain pathways to thalamus and brainstem are completely myelinated by 30th week of gestation while thalamocortical pain fibres in internal capsule and corona radiata get myelinated before term.

Cortical function: Studies of behavioral development, electroencephalography and cerebral metabolism indicate the functional maturity of cerebral cortex in neonates. Electrical signals from cerebral cortex can be recorded as early as 20th week of gestation. Within 2 weeks these ill-sustained patterns become regular. At 30 weeks one can distinguish between awake/sleep patterns on EEG. Cortical components of evoked auditory, visual, olfactory and tactile stimuli are also developed to some extent. Functional maturity of sensory cortex is also suggested by maximal metabolic activity in these areas(16,17).

(*c*) *Neurochemical Development*

Substance-P, a tachykinin involved in transmission and control of pain appears in the spinal cord at 12-16 weeks of gestation. Substance-P containing cells have also been identified in fetal brainstem, hypothalamus, thalamus and cerebral cortex(18).

Endogenous opioides also play a major role in control of pain. Functional endorphinergic cells have been identified in human fetal pituitary at 16 weeks of gestation and earlier. These secrete β-lipoprotein and β-endorphin from 20 weeks onwards. Endogenous opioids are released at birth and in response to fetal/neonatal distress. Strikingly, high concentrations are observed in difficult deliveries, birth asphyxia, apnea and infection either due to the pain and stress of the illness or associated invasive procedures(19,20).

How to Detect Pain in Newborn

Detection of pain is of utmost importance in order to provide pain relief. Currently, assessment of pain in newborn is done by a study of their behavioral and physiological responses (*Table I*).

TABLE I–*Assessment of Pain in Neonates*

Behavioral	Physiological
Body movement(21)	Cardio-respiratory changes(28-31)
Crying(13,22)	Palmar sweating(32)
Facial expressions (11,12,23)	Hormonal and metabolic changes(1)
Complex behavioral responses(24-27)	Vagal tone(9,33)

Behavioral assessment has a high validity and social value but is unlikely to be suitable for those babies who do not demonstrate behavioral changes at all in response to pain either due to their poor general condition, immaturity or sedation. Moreover, behavioral changes are not well standardized and they are subject to personal assessment variation of the observer. Most of the time it is difficult to distinguish between responses to pain and non-painful nociceptive activity.

Physiological responses to pain manifest as cardio-respiratory, hormonal and metabolic alterations. These changes are easier to quantify and are less subjective. But again it is difficult to draw a line between responses to painful and non-painful stimuli. More recently, vagal tone has been gaining importance as an ideal index of neonatal pain but needs to be interpreted cautiously.

Body Movements

It was believed that newborn response to painful stimuli consists of diffuse body movements rather than purposeful responses such as reflex withdrawal. The commonest body reaction to pain is flexion and adduction of the upper and lower limbs associated with grimacing and crying. These responses are quantifiable(21). However, the body movements are not elicitable if the child is restrained or sedated.

Crying

Cry is most widely studied and accepted parameter of neonatal pain. Cry response and its spectrographic analysis has been used as measure of pain(22). With increase in pain, cries become longer, more frequent and higher pitched with less distinct harmonics(13).

Facial Expressions

Awake alert but inactive infants respond with the most facial activity and infants in quiet sleep show least facial reaction and longest latency to cry. Various facial actions such as brow bulge, eye squeeze, nasolabial furrowing, opening of lips, stretching of mouth (vertical and horizonal), pursing of lips, taut tongue and chin quiver have been strictly defined in neonates. Subsequent quantification is done as has been done in adults with simultaneous EMG recordings to decrease subjective nature of judgment(11,12,23).

Complex Behavioral States

Newborns undergoing circumcision without anesthesia are observed to be having (*i*) prolonged periods of NREM sleep, (*ii*) increased wakefulness, (*iii*) irritability, (*iv*) altered arousal levels, and (*v*) altered sleep awake state. Subsequent neurological development and mother-infant social interaction may also be affected by painful procedures carried out in neonatal period. These behavioral changes are not associated with anesthetized neonates undergoing circumcision(24-27).

Cardiorespiratory Changes

Noxious stimuli are associated with an increase in heart rate, whereas non-noxious

stimuli cause bradycardia(28). Heel-lance, lumbar puncture, tracheal intubation are associated with rise in respiratory rate, blood pressure and intracranial pressure(29,30). Transcutaneous partial pressure of oxygen falls during handling of baby and considerably so in neonates undergoing surgical procedures without anesthesia. These changes are not observed if the procedure is carried out under anesthesia(31). Many of these changes are transitory. Severe and prolonged changes are observed in already sick neonates. Thus, procedures which cause considerable drop in T_cPO_2 increase the requirement for supplemental oxygen and may even predispose for chronic pulmonary or neurological sequelae. Needless to say that the role of analgesia/anesthesia in the babies is of unquestionable help.

Palmar Sweating

Palmar sweating is related to emotional factors and is increased by pain and anxiety. The normal values of palmar water loss in a quiet or asleep newborn varies from 10-30 $g/m^2/hr$. Upto four fold increase is observed following painful heel pricks(32).

Hormonal and Metabolic Changes

Isolated elevations in plasma renin, epinephrine, norepinephrine and cortisol levels were observed in minor procedures such as venipuncture, chest physiotherapy and circumcision, respectively. Widespread hormonal alterations occur in major surgeries resulting in breakdown of carbohydrate and fat stores leading to prolonged hyperglycemia and acidosis. Controlled trials have proved the efficacy of halothane and fentanyl anesthesia in full term and preterm infants respectively undergoing surgery. These anesthetics markedly decrease or even abolish the increased secretions of catecholamines, growth hormone, glucagon, cortisol, aldosterone and other corticosteroids, thus minimizing the surgical stress(1).

Vagal Tone

Vagal tone, measurable by analysis of cardiorespiratory patterns and ECG is suggested to be a useful indicator of neonatal pain. It is measured by the amplitude of respiratory sinus arrhythmia extracted from heart period data. Resting vagal tone is useful in differentiating infants with low/high threshold for pain. With increasing invasiveness, vagal tone is reduced. The changes in neonatal vagal tone are also consistent with changes in other behavioral and physiological measures. It is claimed that by vagal tone measurement, one can differentiate between pain and other non painful stress responsiveness. This measure holds great promise for the future and may establish as the basic index to measure neonatal pain. Till then, the search is on for a golden measure by which one can quantify pain in newborns and study the effectiveness of various anesthetics(9,33).

Management

The ability of a newborn to experience and respond to pain has been recognised. It is high time that we gear up to combat the natural or iatrogenic agony and pain suffered by the tiny tot. Various procedures such as sampling, transfusions, lumbar punctures, intubation, aspiration, suction, IV placement, chest tube insertions, arterial and venous catheterization and cutdowns, removal of adhesive tapes and electrodes, chest physiotherapy, *etc.* should be performed gently keeping in mind the associated physiological changes and possible psychological sequelae.

Improved techniques in sampling such as using a mechanical lancet instead of a manual heel prick are advocated(32). The

environment should be improved by lowering the noise and light intensities as far as possible. More time should be allowed for continuous uninterrupted sleep and the babies should be handled minimally. Painful procedures must be restricted and the child should be comforted after invasive procedures(34).

Anesthesia and analgesia should be used in surgical and post-operative patients. Safe anesthetic drugs are now available. Local anesthetics like lidocaine (0.5-1%) or bupivacaine (0.25-0.5%) can be used for local skin infiltration or nerve block, while performing cut downs, chest tube insertion or circumcision. The dosages depend on the type of block performed and the addition of epinephrine to the anesthetic. Lidocaine in a dose of 2-3 mg/kg with 1:200,000 epinephrine or bupivacaine 1 mg/kg with or without epinephrine are safe and relieves physiological and behavioral changes associated with local surgical procedures(35,36).

Fentanyl, a potent and safe drug with unknown mechanism of action can be used for analgesia/anesthesia in the neonate. It blocks nociceptive stimuli, maintains hemodynamic stability and prevents biochemical and endocrinal stresses of surgery. An intravenous dose of 12.5 μg/kg is generally used and can last for around 2 hours. For continuous analgesia, a drip of fentanyl at the rate of 5 μg/kg/hour can be administered(34,37,38). While using analgesia/anesthesia, safety of these drugs, the risk of sedation, common side effects and the risk benefit ratio should be evaluated. In future, pre-operative measurement of vagal tone can be used to determine infants at greater risk for adverse reaction to surgical procedure(33).

Conclusion

Various physiological and behavioral responses to painful stimuli in neonates substantiate their ability to sense pain, which is essential and fundamental for species survival. Biological effects of pain are now being systematically studied in human fetus and neonate. Pain expressions in the newborn just not only reflect tissue damage but is a function of ongoing behavioral state. The lack of awareness regarding this particular topic is amazing and needs furbishing. The ultimate aim should be to keep neonates free from pain and other stressful stimuli as far as possible.

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